Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg)

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Abstract: To prospectively evaluate the associations of dietary calcium and magnesium intake with cancer incidence and mortality, data of 24,323 participants of the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg), who were aged 35-64 years and cancer-free at recruitment (1994-1998), were analyzed using multivariate Cox regression models. After an average follow-up time of 11 years, 2,050 incident cancers were diagnosed and 513 cancer deaths occurred. Dietary calcium intake was inversely but not statistically significantly associated with colorectal cancer risk (hazard ratio [HR] for per 100 mg increase in intake: 0.95; 95% confidence interval [CI]: 0.88, 1.02) and lung cancer risk (HR for per 100 mg increase in intake: 0.94; 95% CI: 0.87, 1.02). No statistically significant associations were observed between dietary calcium intake and site-specific or overall cancer incidence or mortality. Dietary magnesium intake was not statistically significantly associated with any of the investigated outcomes. This prospective cohort study provides no strong evidence to support that high dietary calcium and magnesium intake in the intake range observed in a German population may reduce cancer incidence or mortality.

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Title Page

Title: Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg)

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Abstract page (247 words)

To prospectively evaluate the association of dietary calcium and magnesium intake with cancer incidence and mortality and all-cause mortality, the authors analyzed data of 24,323 participants of the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg), who were aged 35-64 years and cancer-free at recruitment stage (1994-1998), using multivariate Cox regression models. After an average follow-up time of 11 years, 2,050 incident cancers were diagnosed and 513 cancer deaths occurred (all-cause deaths = 1,161). Dietary calcium intake was inversely but not statistically significantly associated with colorectal cancer risk (hazard ratio (HR) for per 100-mg increase of intake: 0.95; 95% confidence interval (CI): 0.88, 1.02) and lung cancer risk (HR for per 100-mg increase of intake: 0.94; 95% CI: 0.87, 1.02). No statistically significant association was observed between dietary calcium intake and total cancer incidence. Compared with participants in the lowest quartile of dietary calcium intake, participants in the highest quartile had an increased risk of all-cause mortality (HR: 1.20; 95% CI: 0.99, 1.45; $P_{\text{trend}} = 0.09$; HR for per 100-mg increase of intake: 1.02; 95% CI: 1.00, 1.05). Dietary magnesium intake was not statistically significantly related to any of the investigated outcomes. This prospective cohort study provides no strong evidence to support the preventive effect of dietary calcium and magnesium intake on cancer incidence and mortality. However, this study suggests a mild adverse effect of dietary calcium intake on all-cause mortality.

Key words: calcium; magnesium; diet; cancer; incidence; mortality

Introduction

Besides the importance in maintaining bone health, calcium is also a key nutrient involving in cell proliferation and carcinogenesis (1;2). Many epidemiological studies have evaluated the association between dietary calcium intake and risks of various cancer types. A growing body of evidence tends to suggest a protective effect of high dietary calcium intake on colorectal cancer (3-8) and breast cancer risk (9-14). Meanwhile, a number of studies have suggested that high calcium intake might increase the risk of prostate cancer (15-21).

Magnesium is another important mineral with various metabolic and physiological functions that influence carcinogenesis (22-24). Although animal studies have consistently suggested an inhibitory effect of dietary magnesium intake on colorectal cancer risk (25-29), available epidemiological findings are few and far from being conclusive (30-33). Relationships between dietary magnesium intake and the risks of other common site-specific cancers have been scarcely reported in literatures.

So far, only one study has reported the association between dietary calcium and magnesium intake and total cancer mortality (34). In that study, dietary calcium intake was not associated with total cancer mortality but significantly inversely associated with all-cause mortality, while dietary magnesium intake was not associated with either total cancer mortality or all-cause mortality.

We hereby reported the associations of dietary calcium and magnesium intake with cancer incidence and mortality in a German prospective cohort.

Methods

Study population

Heidelberg is one of two German areas that joined the European Prospective Investigation into Cancer and Nutrition (EPIC) study. In 1994-1998, 11,928 men (aged 40-64 years) and 13,612 women (aged 35-64 years) were recruited into the EPIC-Heidelberg cohort. The recruitment procedures have been described elsewhere (35). The study protocol was approved by the Ethical Committee of the Heidelberg University Medical School. All participants provided informed consent. In the present study, we excluded participants whose total daily energy intake was in the top or bottom 0.5 sex-specific percentile (men: < 887 / > 5,582 kcal/d; women: < 703 / > 4,381 kcal/d; n = 257) and participants with a diagnosis of cancer at recruitment stage (n = 953), leaving 24,323 participants for analysis.

Assessment of dietary calcium and magnesium intake and other exposures

Diet in the last 12 months before recruitment was assessed using a self-administered food frequency questionnaire (FFQ) that had been validated by 12 24-hour dietary recalls (36;37). Dietary intakes of nutrients were derived using the German Dietary Nutrient Database BSL, version II.3. For the entire EPIC-Germany cohort, the main dietary sources of calcium were milk/milk products (39.9% for men and 38.7% for women) and non-alcoholic beverages (28.2% for men and 34.4% for women); the main dietary sources of magnesium were non-alcoholic beverages (25.1% for men and 33.7% for women) and cereal foods (22.6% for men and 20.6% for women) (38). Regular use of dietary supplements in the last 4 weeks before recruitment was assessed. However, dosage data were not collected. Baseline demographic, lifestyle and other health-related data were collected in a face-to-face interview and a questionnaire survey.

Ascertainment of disease outcomes

Incident diseases and deaths that occurred during follow-up were reported by study participants or their next of kin in regular follow-up questionnaire surveys. Reported incident diseases were verified by reviewing medical records from hospitals. For deceased participants, the underlying cause of death was obtained from the official death certificate. In the present study, disease endpoints, coded using the International Classification of Disease (10^{th} Revision, ICD-10), included: incident colorectal cancer (C18-C20), incident lung cancer (C34), incident prostate cancer (C61); incident breast cancer (C50); total cancer incidence and mortality (B21 and C00-C97), and all-cause mortality.

Statistical analyses

The residual method (39) was used to adjust dietary nutrient intakes for total energy intake. We categorized energy-adjusted dietary calcium and magnesium intake into quartiles using sex-specific cut-off points. To compare age-adjusted baseline characteristics across quartiles, we performed analysis of covariance and logistic regression (40). Multivariate Cox regression models were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for both quartiles and per 100-mg increase of dietary calcium and magnesium intake. For the former, likelihood ratio tests were performed to test the statistical significance of linear trend, with medians of quartiles modeled as a continuous variable. For the latter, energy-adjusted calcium and magnesium intake were divided by 100 so that one unit represented an actual intake of 100 mg. Multivariate models adjusted for the following confounders: sex, age at recruitment (years), educational level (none/primary, technical/secondary, and university), physical activity (inactive, moderately inactive, moderately active, and active (41)), body mass index (BMI, kg/m^2), waist-to-hip ratio, smoking categories (never smoker; former smoker, quit ≥ 10 years, quit < 10 years; and current smoker, ≤ 10, 11-20, > 20 cigarettes/d), lifetime alcohol intake (g/d), dietary fiber intake (g/d), meat/meat product intake (g/d), and total energy intake (kcal/d). All these confounders, with exception of sex and calcium/vitamin D supplementation, altered the exposure-disease effect for 5% or greater. For the analysis of dietary calcium intake, dietary vitamin D and K_2 intake (µg/day) and regular use of calcium/vitamin D supplements (yes/no) were additionally adjusted for. The reason for adjusting for dietary vitamin K_2 intake is that vitamin K_2 intake, which closely correlates with dietary calcium intake ($r = 0.63$), was significantly inversely associated with lung and prostate cancer incidence and total cancer mortality in our cohort (42).

For total cancer incidence and mortality and all-cause mortality, we further performed a sex-specific analysis and two-year lag analysis by excluding cancer cases or deaths that occurred in the first 2 years of follow-up. Two-sided $P < 0.05$ was considered statistically significant. SAS software (version 9.2; SAS Institute, Cary, NC) was used to perform all statistical analyses.

Results

Age-adjusted baseline characteristics of participants are shown in Table 1. Participants with higher dietary calcium and magnesium intake were more likely to have a university degree, to be physically active, and to regularly take calcium/vitamin D supplements. Participants with higher dietary calcium intake also had a shorter smoking duration and a lower lifetime alcohol intake. Higher dietary calcium and magnesium intake were associated with certain favorable dietary factors, such as a higher dietary intake of vitamin D, fiber, but a lower intake of meat/meat products and total energy.

During an average follow-up time of 11 years, 2,050 incident cancer cases were diagnosed and 513 cancer deaths occurred (all-cause deaths = 1,161). Dietary calcium intake in quartiles was not statistically significantly associated with total or common site-specific cancer (colorectum, lung, prostate, and breast) incidence and total cancer mortality (Table 2). For all-cause mortality, participants in the highest quartile of dietary calcium intake had an increased risk of all-cause mortality than did those in the lowest quartile (HR: 1.20; 95% CI: 0.99, 1.45). We also ran models without adjusting for vitamin K_2 intake, which revealed a statistically significantly inverse association of dietary calcium intake with lung cancer risk (HR for highest versus lowest quartile: 0.61; 95% CI: 0.38, 0.98; $P_{trend} = 0.02$), a non-significantly inverse association with prostate cancer risk (HR highest versus lowest quartile: 0.77; 95% CI: 0.56, 1.05; $P_{trend} = 0.07$), and a non-significantly inverse association with total cancer mortality (HR for highest versus lowest quartile: 0.79, 95% CI: 0.61, 1.02; $P_{trend} = 0.07$). When treated as a continuous variable, per 100-mg increase of dietary calcium intake was inversely yet not statistically significantly associated with colorectal cancer risk (HR: 0.95; 95% CI: 0.88, 1.02) and lung cancer risk (HR: 0.94; 95% CI: 0.87, 1.02). For all-cause mortality, the association was positive and borderline significant (HR: 1.02; 95% CI: 1.00, 1.05).

As shown in Table 3, dietary magnesium intake, either in quartiles or as a continuous variable, was not statistically significantly associated with cancer incidence and mortality and all-cause mortality. For site-specific cancer incidence, per 100-mg increase of dietary magnesium intake was inversely but not statistically significantly associated with lung cancer risk (HR: 0.75; 95% CI: 0.51, 1.11).

The sex-specific analysis and 2-year lag analysis did not produce substantially different results (data not shown).

Discussion

After an average follow-up time of 11 years of the EPIC-Heidelberg cohort, we observed a statistically non-significantly inverse association of dietary calcium intake with colorectal and lung risk and a borderline significant positive association with all-cause mortality. There were no statistically significant associations between dietary magnesium intake and cancer incidence and mortality and all-cause mortality.

Dietary calcium intake

In the present study, dietary calcium intake was not associated with total cancer incidence, in contrast to a previous study showing a significantly inverse association in women but not in men (43). In our cohort, there was no statistically significant effect modification by sex (data not shown). Two meta-analyses of observational and interventional studies consistently suggest that high dietary calcium intake may reduce colorectal cancer risk (3;44). A possible mechanism for this protective effect is that free calcium in colon can bind bile acids and fatty acids and consequently prohibit the proliferation and differentiation of colorectal epithelial cell (45-49). In the present study, although we observed no significantly inverse association between the energy-adjusted dietary calcium intake and colorectal cancer risk, the absolute dietary calcium intake was significantly inversely associated with colorectal cancer risk, according to the standard model that controlled for total energy intake as a confounder (HR for highest versus lowest quartile: 0.46, 95% CI: 0.26, 0.79; $P_{\text{trend}} = 0.01$).

The relationship between dietary calcium intake and lung cancer risk has been rarely reported. Our finding of this non-significantly inverse association is not in agreement with the results of two previous observational studies, which showed either a significant positive association or a null association (43;50). However, in the model that ignored dietary vitamin K_2 intake, the association was statistically significant, suggesting a confounding effect of dietary vitamin K_2.

We observed no statistically significant association between dietary calcium intake and prostate cancer risk, consistent with the result of a meta-analysis of 45 observational studies (51), but not in line with the significant positive association reported in another meta-analysis of 10 prospective cohort studies, in which the median dietary calcium intake of the highest category ranged from 1,329 to 2,250 mg/d (21). In the EPIC-Heidelberg cohort, the median dietary calcium intake of the highest quartile was 1,132 mg/d. We may assume that only very high calcium intake can increase prostate cancer risk. However, a cohort study of Chinese men has suggested that dietary calcium intake may increase prostate cancer risk even at a substantially low level (52), implying that the real dose-response relationship could be complicated. On the other hand, the primary source of calcium in western diets is milk and milk products. Besides calcium, some other dairy components, such as saturated fatty, dairy protein, and hormone, are also risk factors for prostate cancer (15;53;54) and therefore may confound the association between dietary calcium intake and prostate cancer risk. In the present study, however, adjustment for milk/milk product intake did not substantially change the association, and milk/milk product intake itself was not statistically significantly associated with prostate cancer risk either. Some studies have suggested that high dietary calcium intake might have a more pronounced adverse effect on advanced/fatal prostate cancer risk (20;55;56). However, the present study observed no such a result (data not shown). Again, dietary vitamin K_2 had a confounding effect on the association between dietary calcium intake and prostate cancer risk, which was suggested by the strengthened inverse association in the vitamin K_2-unadjusted model.

We observed no significantly inverse association between dietary calcium intake and breast cancer risk as was observed in previous studies (9-14). Some of these studies showed that the inverse association was more pronounced for premenopausal women (10, 11, 13, 14). In the present study, however, menopausal status did not modify the null association (data not shown).

In the present study, the vitamin K2-unadjusted model produced an inverse association between dietary calcium intake and total cancer mortality, not supporting the null association reported in one prospective study of Swedish men (34). In our cohort, dietary vitamin K_2 intake was significantly inversely associated with overall cancer morality (HR for highest vs. lowest quartile: 0.72; 95% CI: 0.53, 0.85; ptrend = 0.03) (42). The substantially attenuated inverse association due to the adjustment for dietary vitamin K_2 intake suggests that dietary calcium intake may have no independent effect on overall cancer mortality. It is also notable that the mean energy-adjusted dietary calcium intake in the Swedish male cohort was much higher than that in our cohort (1,400 vs. 784 mg/day for the entire cohort and 795 mg/day for the sub-cohort of men). In such a population that is less likely to have suboptimal calcium supply, an independent effect of dietary calcium intake, assuming it really exists, may be more difficult to detect.

Dietary magnesium intake

To the best of our knowledge, the association between dietary magnesium intake and total cancer incidence has never been reported before, and therefore the null association that we observed here needs to be confirmed or refuted by others. For site-specific cancer incidence, our result supports the finding of a Dutch cohort study that dietary magnesium intake was not associated with colorectal cancer risk (33). Other three prospective cohort studies of women reported either a significantly inverse association or a null association (30-32). The average energy-adjusted dietary magnesium intake of these women cohorts were 289, 232, and 329 mg/d, respectively, comparable to that of our female sub-cohort (288 mg/d). However, the small number of incident colorectal cancer cases in our cohort does not permit a meaningful separate analysis for women.

So far, only very few epidemiological studies have evaluated the association between dietary magnesium intake and lung, prostate, and breast cancer risk. In one case-control study, dietary magnesium intake was significantly inversely associated with lung cancer risk (57). In the present study, the association was inverse but not statistically significant. Another case-control study showed a moderate inverse association between magnesium level in drinking water and prostate cancer mortality (58). However, the relationship for magnesium intake from food has never been reported. As the present study suggested, dietary magnesium intake might have no association with prostate cancer risk, whether for overall prostate cancer or for advanced and non-advanced types separately. The null association of dietary magnesium intake with either cancer mortality or all-cause mortality in the present study is in agreement with the result of the Swedish male cohort (34). Based on limited findings, it seems that dietary magnesium intake might have no effect on cancer incidence and mortality. However, a solid conclusion could not be drawn until more evidence becomes available.

Several limitations of the present study should be noted. Firstly, FFQ, even though it is usually validated before application, is a relatively rough instrument to quantify dietary intakes of nutrients and thus the measurement errors are difficult to eliminate. Secondly, as shown in the present study, participants with higher dietary calcium intake were more likely to take calcium supplements. However, calcium intake from supplements was not quantified. In addition, not taking into account calcium intake from drinking water might also be problematic, although we have no knowledge on its relationship with calcium intake from foods. Lastly, some important cancer risk factors, such as family history and cancer screening, were not adjusted for in the present study, and therefore residual confounding may exist. However, we additionally adjusted for dietary vitamin K_2 intake, an important confounder that had not been controlled for in any of previous studies.

In summary, this German prospective cohort study provides no strong evidence to support that high dietary calcium and magnesium intake in the intake range observed in a German population may reduce the risk of cancer incidence, in total or for common site-specific types, and overall cancer mortality.

Acknowledgments This study was funded by the Deutsche Krebshilfe [Grant-No.: 70-488-Ha I] and the Graduiertenkolleg 793: Epidemiology of communicable and chronic non-communicable diseases and their interrelationships. The authors declare no conflict of interest.

Table 1. Age-adjusted baseline characteristics of the EPIC-Heidelberg participants by sex-specific quartiles of dietary calcium and magnesium intake, 1994-1998

	Quartiles of calcium intake				Quartiles of magnesium intake			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
No. of participants (*n*)	6,070	6,095	6,072	6,086	6,143	6,039	6,048	6,093
Men (%)	47.0	47.0	46.8	47.0	46.9	47.8	46.7	46.4
Age at recruitment (years)	51.3	50.7	50.4	50.7	50.1	50.7	51.0	51.2†
University degree (%)	21.2	28.6	33.0	37.6†	22.2	29.9	32.6	35.8†
Physically active (%)	22.4	24.0	24.2	28.8†	22.0	23.2	24.7	29.5†
BMI (kg/m^2)	26.2	26.2	26.1	26.0†	26.3	26.2	26.2	25.8†
Waist-to-hip ratio	0.87	0.87	0.87	0.86†	0.87	0.87	0.87	0.86†
Smoking duration (years)	13.6	12.0	11.8	11.8†	12.4	12.0	12.3	12.5
Lifetime alcohol intake (g/d)	21.7	17.8	15.6	13.9†	15.4	16.9	17.9	18.6†
Dietary calcium intake (mg/d)[a]	512	675	820	1,131†	655	745	808	930†
Dietary magnesium intake (mg/d)[a]	293	308	322	345†	261	299	328	381†
Vitamin D (µg/d)[a]	3.0	3.3	3.3	3.4†	3.2	3.2	3.3	3.3†
Vitamin K_2 (µg/d)[a]	28.0	33.5	37.9	44.3†	36.6	37.0	35.8	34.2†
Dietary fiber (g/d)[a]	18.4	19.9	20.5	21.0†	16.6	18.7	20.6	24.0†
Meat/meat product intake (g/d)	119.7	103.8	92.1	76.4†	110.2	106.3	96.5	77.8†
Total energy intake (kcal/d)	1,974	1,971	1,929	1,954†	1,960	1,957	1,961	1,950
Regular use of Ca/vitamin D supplements[b], (%)	7.5	8.3	9.6	11.5†	7.4	8.4	9.4	11.4†

Participants with a diagnosis of cancer at recruitment and participants whose total daily energy intake was in the top or bottom 0.5 sex-specific percentile (men: < 887 / > 5,582 kcal/d; women: < 703 / > 4,381 kcal/d) were excluded.

BMI body mass index; *EPIC* European Prospective Investigation into Cancer and Nutrition

† $P_{trend} < 0.05$, tested by using Cochran-Armitage method for categorical variables and generalized linear model for continuous variables. Values are means or percentages.

[a] Adjusted for total energy intake using the residual method.

[b] Including multivitamins/minerals.

Table 2. Multivariate HRs and 95% CIs for cancer incidence by quartiles of dietary calcium intake in the EPIC-Heidelberg cohort, 1994-2010

	Quartiles of dietary calcium intake					Intake as
	Q1	Q2	Q3	Q4	P_{trend}	continuous variable[a]
Overall cancer incidence						
No. of cases	555	511	489	495		
HR (95% CI)	1.00 (ref)	1.01 (0.89-1.15)	1.01 (0.89-1.16)	1.04 (0.90-1.20)	0.75	1.01 (0.99-1.03)
Colorectal cancer						
No. of cases	59	55	47	40		
HR	1.00 (ref)	1.03 (0.71-1.52)	0.93 (0.61-1.42)	0.80 (0.50-1.30)	0.32	0.95 (0.88-1.02)
Lung cancer						
No. of cases	67	28	25	27		
HR (95% CI)	1.00 (ref)	0.66 (0.41-1.05)	0.64 (0.38-1.07)	0.71 (0.41-1.21)	0.50	0.94 (0.87-1.02)
Prostate cancer						
No. of men	2,854	2,866	2,840	2,861		
Mean intake (mg/d)	510	678	830	1163		
No. of cases	102	103	98	84		
HR (95% CI)	1.00 (ref)	1.07 (0.80-1.42)	1.04 (0.77-1.41)	0.83 (0.58-1.18)	0.23	0.99 (0.94-1.03)
Breast cancer						
No. of women	3,216	3,229	3,232	3,225		
Mean intake (mg/d)	515	673	812	1102		
No. of cases	102	99	106	108		
HR (95% CI)	1.00 (ref)	0.95 (0.72-1.27)	0.98 (0.73-1.31)	0.98 (0.71-1.35)	0.93	1.02 (0.97-1.06)
Total cancer mortality						
No. of cases	173	118	113	109		
HR (95% CI)	1.00 (ref)	0.85 (0.66-1.08)	0.88 (0.68-1.15)	0.90 (0.68-1.20)	0.52	0.98 (0.95-1.03)
All-cause mortality						
No. of cases	350	288	240	283		
HR (95% CI)	1.00 (ref)	1.03 (0.88-1.22)	0.96 (0.80-1.14)	1.20 (0.99-1.45)	0.09	1.02 (1.00-1.05)

Adjusted for sex, age at recruitment, educational level, physical activity, BMI, waist-to-hip ratio, smoking category, lifetime alcohol intake, meat/meat product intake, dietary intakes of vitamin D, vitamin K_2, and fiber, total energy intake and regular use of Ca/vitamin D supplements. For lung cancer incidence, dietary magnesium intake was additionally adjusted for.Abbreviations:

BMI body mass index; *EPIC* European Prospective Investigation into Cancer and Nutrition, *HR* hazard ratio.

Participants with a diagnosis of cancer at recruitment and participants whose total daily energy intake was in the top or bottom 0.5 sex-specific percentile (men: < 887 / > 5,582 kcal/d; women: < 703 / > 4,381 kcal/d) were excluded.

[a] For per 100-mg increase of dietary calcium intake.

Table 3. Multivariate HRs and 95% CIs for cancer incidence by quartiles of dietary magnesium intake in the EPIC-Heidelberg cohort, 1994-2010

	Quartiles of dietary magnesium intake					Intake as
	Q1	Q2	Q3	Q4	P_{trend}	continuous variable[a]
Overall cancer incidence						
No. of cases	513	505	463	569		
HR (95% CI)	1.00 (ref)	0.99 (0.88-1.13)	0.90 (0.79-1.03)	1.12 (0.97-1.29)	0.19	1.06 (0.95-1.18)
Colorectal cancer						
No. of cases	48	54	51	48		
HR	1.00 (ref)	1.18 (0.79-1.76)	1.18 (0.76-1.81)	1.27 (0.76-2.10)	0.41	1.14 (0.78-1.68)
Lung cancer						
No. of cases	47	34	34	32		
HR (95% CI)	1.00 (ref)	0.80 (0.51-1.26)	0.88 (0.55-1.42)	0.83 (0.49-1.43)	0.52	0.75 (0.51-1.11)
Prostate cancer						
No. of men	2,883	2,887	2,824	2,827		
Mean intake (mg/d)	287	330	362	421		
No. of cases	88	108	84	107		
HR (95% CI)	1.00 (ref)	1.19 (0.89-1.58)	0.91 (0.66-1.25)	1.07 (0.76-1.49)	0.96	0.96 (0.76-1.21)
Breast cancer						
No. of women	3,260	3,152	3,224	3,266		
Mean intake (mg/d)	235	271	298	347		
No. of cases	113	101	90	111		
HR (95% CI)	1.00 (ref)	0.93 (0.70-1.22)	0.77 (0.57-1.04)	0.97 (0.69-1.35)	0.68	0.90 (0.67-1.20)
Total cancer mortality						
No. of cases	139	109	127	138		
HR (95% CI)	1.00 (ref)	0.80 (0.62-1.03)	0.95 (0.74-1.23)	1.04 (0.79-1.36)	0.62	1.04 (0.85-1.28)
All-cause mortality						
No. of cases	321	267	285	288		
HR (95% CI)	1.00 (ref)	0.88 (0.75-1.04)	0.99 (0.84-1.17)	1.04 (0.87-1.25)	0.41	1.09 (0.95-1.25)

Adjusted for sex, age at recruitment, educational level, physical activity, BMI, waist-to-hip ratio, smoking category, lifetime alcohol intake, meat/meat product intake, dietary intake of fiber, and total energy intake. For colorectal, lung, and prostate cancer incidence and total cancer mortality, dietary calcium and vitamin K_2 intake were additionally adjusted for.

Participants with a diagnosis of cancer at recruitment and participants whose total daily energy intake was in the top or bottom 0.5 sex-specific percentile (men: < 887 / > 5,582 kcal/d; women: < 703 / > 4,381 kcal/d) were excluded.

BMI body mass index; *EPIC* European Prospective Investigation into Cancer and Nutrition, *HR* hazard ratio.

[a] For per 100-mg increase of dietary magnesium intake.

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